

REMARKS

Applicants respectfully request the Examiner to reconsider the present application in view of the foregoing amendments to the claims and the following remarks.

Status of the Claims

Claims 1-21, 23, 24, 26-28 and 30-45 are currently pending in the present application. The Office Action is non-final. Claims 21 and 23 have been amended without prejudice or disclaimer. No new matter has been added by way of amendment. For instance, claims 21 and 23 have been simplified to further clarify the invention. As indicated by the Examiner (see page 3, first paragraph, of the Office Action dated June 27, 2008; hereinafter "Office Action"), further support for claims 21 and 23 can be found within SEQ ID NO: 23 in the Sequence Listing of the present specification. Thus no new matter has been added.

Based upon the above considerations, entry of the present Amendment is respectfully requested.

Issue Under 35 U.S.C §112, First Paragraph, Written Description

Claims 21-23 stand rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. The Examiner asserts that the claims contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor was in possession of the claimed invention at the time the application was filed.

Applicants have cancelled claim 22, thus obviating the rejection as to this claim.

Additionally, Applicants have amended claims 21 and 23, without prejudice or disclaimer, so that it is clear that the promoter is not positioned as a tandem arrangement. The sequence of 1 to 5484 of SEQ ID NO: 23 comprises a fibroin H chain promoter and its upstream region, and fibroin H chain 5'-terminal region (first exon, first intron and a part of the second exon). As indicated above, the Examiner also states that the amended claims have support within the specification since the Examiner indicated that nucleotides 1-5484 of SEQ ID NO: 23 are present in the Sequence Listing of the instant specification.

In light of the above and the amended claims 21 and 23, Applicants, at the time of filing, were in possession of the claimed invention.

Applicants respectfully request reconsideration and withdrawal of the present rejection.

Issues Under 35 U.S.C. § 103(a), Obviousness

Claims 21-24, 26-28, 30-39 and 42-45 stand rejected under 35 U.S.C. § 103(a) as being unpatentable as obvious over Liu *et al.*, U.S. Patent Application Publication No. 2002/0137211, (hereinafter, "Liu"), in view of Zhao *et al.*, *Acta Biochimica et Biophysica Sinica*, 33(1):112-116, 2001 (hereinafter, "Zhao"), Zhang *et al.*, *Acta Biochimica et Biophysica Sinica*, 31(2):119-123, 1999 (hereinafter, "Zhang"), and GenBank Acc. No. AF226688.

The Examiner asserts that SEQ ID NO:23 was previously examined by the Examiner as it was recited in claim 26. The Examiner states that SEQ ID NO:23 is disclosed in Zhao and GenBank Accession No. 226688 and that the arrangement of the various elements is also disclosed therein.

The Examiner further asserts that Zhao discloses a transgenic silkworm with a genome comprising a “gene cassette” embraced by the instant claims, which comprises, in order, the 5' end of the endogenous fibroin H-chain gene, including the promoter. Additionally the Examiner suggests that the structural organization and sequence of the *Bombyx mori* fibroin heavy chain gene and its promoter was known in the prior art as GenBank Accession No. AF 226688, and there is no reason for a person of ordinary skill in the art to utilize a minimal promoter region with low expression activity as part of a gene cassette to express a gene of interest in the silk gland. The Examiner also asserts that a person of ordinary skill in the art having utilized the promoter sequences as set forth in SEQ ID NO: 23 in a gene cassette would necessarily include nucleotides 57444 to 62927 of GenBank Accession No. AF 226688.

Applicants have cancelled claim 22, thus obviating the rejection as to this claim. Applicants respectfully traverse as to the remaining claims.

Graham v. John Deere, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), has provided the controlling framework for an obviousness analysis. A proper analysis under § 103(a) requires consideration of the four *Graham* factors of: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims that are at issue; resolving the level of ordinary skill in the pertinent art; and evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. at 17, 148 USPQ at 467.

M.P.E.P. § 2143 sets forth the guidelines in determining obviousness. But before the Examiner can utilize these guidelines, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*; *supra*. To reject a claim based on the above mentioned guidelines, the Examiner must resolve the *Graham* factual inquiries. MPEP §2143.

If the Examiner resolves the *Graham* factual inquiries, then the Examiner has to provide some rationale for determining obviousness, wherein M.P.E.P. § 2143 sets forth the rationales that were established in *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

Applicants respectfully submit that the Examiner has not appropriately resolved the *Graham* factors, including the factors of determining the scope and content of the prior art and ascertaining the differences between the prior art and the claims that are at issue. Based on the following, Applicants maintain that the above mentioned *Graham* factors actually reside in Applicants' favor. Additionally, Applicants submit that since the Examiner did not resolve the *Graham* factors, the rationale the Examiner provides for combining the cited references is improper.

Applicants respectfully submit that the present invention is distinct from the cited references. As can be seen from paragraph (2) of amended claim 21, the gene cassette of the present invention contains a sequence enhancing an activity of a fibroin H chain promoter and a sequence enhancing an expression of an exogenous gene under the control by the fibroin H chain promoter.

The present inventors studied a gene cassette which enhances the expression of an exogenous gene when the exogenous gene is expressed under the control by a fibroin H chain promoter using a piggyBac transposon in a transgenic silkworm. As a result, the present inventors found, for the first time, that a sequence of 5'-terminal side of fibroin H chain gene, as described in paragraph [0062] of the present application, that "In the gene cassette for expressing an exogenous protein in the present invention, the 5' terminal portion of fibroin H chain gene is a

DNA sequence having action that enhances expression of exogenous protein gene by a promoter.”

In addition, as can be seen from the description in paragraph [0062] of the present application, which reads “In addition, as the region upstream from the 5’ side of fibroin H chain gene promoter, namely a roughly 5.5 kbp upstream region, is considered to be the region that enhances promoter activity,” the present inventors found that the activity of the fibroin H chain promoter can be enhanced by combining a fibroin H chain promoter and its upstream sequence (total about 5.5 kbp). In addition, the present inventors found that these elements are essential for expression of an exogenous gene using the piggyBac transposon in the silk gland of a transgenic silkworm. Hence, the present invention was completed on the basis of the above-mentioned new findings.

On the other hand, the gene cassette disclosed in the Liu reference uses fibroin L chain (not H chain as in the present invention), and does not describe or suggest the above-mentioned features of the present invention.

Next, in regards to the Liu and Zhao references, Zhao and Zhang describe a gene cassette containing a 5’ terminal sequence of fibroin H chain. However, the purpose of the sequence is in the construction of a transgenic silkworm by homologous recombination of genes. Zhao and Zhang do not describe or suggest that the sequence in question has a function for enhancing expression of an exogenous gene in the silk gland. Additionally, the gene cassette of Zhao and Zhang does not contain a region enhancing the expression of promoter activity, upstream of the fibroin H chain promoter.

Also, the Examiner asserts that if genomic sequences around the fibroin H chain gene are known in GenBank Accession No. AF226688, "There is no reason for a person of ordinary skill in the art to utilize a minimal promoter region with low expression activity as part of a gene cassette to express a gene of interest in the silk gland."

Applicants respectfully disagree. In the field of the biotechnology, generally, it is well known in the art that there is a high level of unpredictability. Further, none of the disclosures of the references provide any rationale for identification of a specific region having a specific function from a genomic sequence. There would be no reasonable expectation of success since there is no finite set of solutions.

For example, for the present invention, the identification of an upstream region of the fibroin H chain promoter, which enhances the expression of an exogenous gene in the silk gland on the basis of genomic sequence information, was not predictable. Finding a region of a 5' terminal side of the fibroin chain gene enhances the expression of an exogenous gene required a high level of the creativity due to the unpredictable nature of gene expression from a gene construct. Therefore, the Examiner's assertion is incorrect.

As can be seen from the above, if the transgenic silkworm construction system using piggyBac transposon described in the Liu reference and the gene cassette described in the Zhao and Zhang references, there is a level of unpredictability that a skilled artisan would not be able to predict that a sequence of 5' terminal side of the fibroin H chain gene is essential for enhanced expression of an exogenous gene.

In addition, due to the unpredictable nature in the art, the combined teachings of the Liu reference and the genomic information around the fibroin H chain gene disclosed in Genbank

Accession No. AF226688 would not render the present invention obvious since a skilled artisan would not have identified an upstream sequence of the fibroin H chain promoter that provides enhancement of the expression of an exogenous gene.

The courts since *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), have recognized that inventors face additional barriers in relatively unpredictable technological areas as noted in *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, ; *supra* (since TSM test can provide helpful insight if it is not applied as rigid and mandatory formula, and since, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led chemist to modify known compound, in particular manner, in order to establish *prima facie* obviousness of new compound). This is applicable to the biochemical arts. The cited references need to identify some reason that would have led a biochemist/biologist to modify the cited references, in particular manner, in order to establish *prima facie* obviousness of the present invention. There is no disclosure within the cited references that would lead the biochemist/biologist to identify the upstream region of the fibroin H chain promoter, which enhances the expression of an exogenous gene in the silk gland on the basis of genomic sequence information, from an infinite set of sequences.

As indicated above, the present application shows that the activity of the fibroin H chain promoter can be enhanced by combining a fibroin H chain promoter and its upstream sequence (total about 5.5 kbp). In addition, the present inventors found that these elements are essential for expression of an exogenous gene using the piggyBac transposon in the silk gland of a transgenic silkworm. On the other hand, the gene cassette disclosed in the Liu reference uses fibroin L chain (not H chain as in the present invention), and does not describe or suggest the

above-mentioned features of the present invention (as admitted by the Examiner on page 7 of the previous Office Action dated April 18, 2007). Zhao and Zhang describe a gene cassette containing a 5' terminal sequence of fibroin H chain. However, the purpose of the sequence is in the construction of a transgenic silkworm by homologous recombination of genes. Zhao and Zhang do not describe or suggest that the sequence in question has a function for enhancing expression of an exogenous gene in the silk gland. Additionally, the gene cassette of Zhao and Zhang does not contain a region enhancing the expression of promoter activity, upstream of the fibroin H chain promoter.

In light of the above presently amended claims and remarks, because there is no disclosure, teaching, suggestion, reason or rationale provided in the cited references that would allow one of ordinary skill in the art to arrive at the instant invention as claimed, it follows that the same references are incapable of rendering the instant invention obvious under the provisions of 35 USC § 103(a). Based upon the above, and applying the *Graham factors* analysis test, it is submitted that a *prima facie* case of obviousness has not been established. Applicants respectfully request reconsideration and subsequent withdrawal of the above rejections.

In view of the above remarks, Applicants believe the pending application is in condition for allowance.

CONCLUSION

A full and complete response has been made to all issues as cited in the Office Action. Applicants have taken substantial steps in efforts to advance prosecution of the present application. Thus, Applicants respectfully request that a timely Notice of Allowance issue for the present case.

In view of the above remarks, it is believed that claims are allowable.

Should there be any outstanding matters within the present application that need to be resolved, the Examiner is respectfully requested to contact Paul D. Pyla, Reg. No. 59,228, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By 

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